An Introduction to Cannabinoids in Clinical Practice

Danial Schecter, MD, CCFP
Executive Director,
Cannabinoid Medical Clinic

OEMAC
Occupational and Environmental Medical Association of Canada

September 28th, 2015
DISCLOSURE OF COMMERCIAL SUPPORT

- This program has not received any financial support
Faculty: Danial Schecter

Relationships with commercial interests:
- Honoraria: CanniMed, Tilray, Tweed, MariCann
- Consulting Fees: Canabo Medical Corporation
- Medical Advisory Board: Tweed
Learning Objectives

- Conceptualize the endocannabinoid system and function
- Review cannabinoid availability in Canada including both prescription cannabinoids and herbal cannabis
- Understand the Canadian regulations regarding the use of cannabis for medical purposes
Why Cannabinoid Medicine

• Became aware of the Endocannabinoid System
• Realization that traditional pharmaceutical agents had limited efficacy or intolerable side effects
• Listened to stories of patients who achieved real benefit with improved quality of life
Cannabinoids… A Class of Its Own

- Cannabinoids should be considered a **Therapeutic Class**
- Cannabinoids are considered a third line agent for chronic neuropathic pain (CPS 2014 guidelines)

---

**CONSENSUS STATEMENT**

Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society

DE Moulin MD, A Boulanger MD, AJ Clark MD, H Clarke MD PhD, T Dao DMD PhD, CA Finley MD, A Forlan MD PhD, J Gilron MD MSc, A Gordon MD, PK Horley-Forster MD, BJ Sende MD PhD, P Square MD, J Stinson RN PhD, P Tannen PhD, A Velly DDS PhD, MA Ware MD, EL Weinberg MD, CD Williamson MBB5
Some Definitions

- **Cannabinoids** are a class of compounds that act on cannabinoid receptors in the human body.
- **Endocannabinoids** are cannabinoids that are naturally produced in the body (endogenous).
- **Phytocannabinoids** are cannabinoids produced by the cannabis plant.
- **Synthetic cannabinoids** are laboratory-synthesized compounds that bind to cannabinoid receptors:
  - Some are used as pharmaceuticals (e.g., Nabilone).
  - Many are research tools.
  - Some are used as street drugs (e.g., “Spice” and “K2”).
The Endocannabinoid System

- Lipid signaling system
- Important regulatory function in physiologic and pathophysiologic processes including:
  - Neural development
  - Immune function
  - Inflammation
  - Appetite
  - Metabolism and energy homeostasis
  - Cardiovascular function
  - Digestion
  - Bone development and bone density
  - Synaptic plasticity and learning
  - Pain
  - Reproduction
  - Psychiatric disease
  - Psychomotor behavior
  - Memory
  - Wake/sleep cycles
  - Regulation of stress and emotional state
The Endocannabinoid System

Components of the endocannabinoid system:

• Endogenous Cannabinoids:
  • Anandamide or AEA (“Ananda” = Sanskrit for “bliss”)
  • 2-arachidonyl-glycerol or 2-AG

• Cannabinoid Receptors:
  • CB-1 – Found in the CNS/PNS/GI Systems
  • CB-2 – Found in the Immune System

• Degrading enzymes:
  • FAAH
  • MAGL
The Endocannabinoid System
Distribution of CB1 Receptors

Green shading represents cannabinoid receptors in the body:

- CNS
- PNS
- Intestine
- Liver
Distribution of CB1 Receptors

cerebral cortex
- decision making, cognition, & emotional behavior
caudate nucleus
- learning & memory system
putamen
- regulate movements & influence various types of learning
globus pallidus
- regulate voluntary movements
amygdala
- responsible for anxiety & stress, emotion & fear, pain
hypothalamus
- body temperature, feeding, neuroendocrine function
hippocampus
- memory & learning
substantia nigra
- important role in reward, addiction, & movement
cerebellum
- motor control & coordination
dorsal vagal complex
- emesis
Therapeutic Index

Therapeutic Index:

Comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes toxicity.

Cannabis 1000:1
Diazepam 100:1
Morphine 70:1
Cocaine 15:1
Alcohol 10:1
Digoxin 2:1
LD50 Cannabis

• “At present it is estimated that marijuana’s LD-50 is around 1:20 000 or 1:40 000. In layman terms this means that in order to induce death a marijuana smoker would have to consume 20 000 to 40 000 times as much marijuana as is contained in one marijuana cigarette. NIDA-supplied marijuana cigarettes weight approximately .9 grams. A smoker would theoretically have to consume nearly 1 500 pounds of marijuana within fifteen minutes to induce a lethal response.”
Cannabinoids and Pain Pathways

CB1 receptors are located in well-known pain processing pathways. The receptors (e.g. skin nociceceptor) are present in peripheral terminals of primary sensory neurons (1), at synapses in the spinal cord (2) and in pain processing areas of brain.

At synapses (2), CB1 receptors may modulate presynaptic neurotransmission of nociceptive information by inhibiting the release of excitatory neurotransmitters.
What is in Marijuana?

Cannabis (Sativa, Indica, or Ruderalis)

Marijuana (dried leaves and flowering heads)

More than 400 chemical compounds

Isolated pure compounds

Non-cannabinoids

Psychoactive
- $\Delta^9$-THC
- $\Delta^8$-THC
- cannabinol (weak)

Cannabinoids

Active but not psychoactive
- Cannabidiol (CBD)

Inactive
- more than 60 compounds

More than 80 types of cannabinoids

Kalant 2001
# The Major Cannabinoids

<table>
<thead>
<tr>
<th>∆9-THC</th>
<th>CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Partial CB1 and CB2 receptor agonant</td>
<td>• Partial antagonist of CB1 and CB2</td>
</tr>
<tr>
<td>• Responsible for the psychoactive effects of cannabis</td>
<td>• Not psychoactive</td>
</tr>
<tr>
<td>• Effective for relief of acute pain and muscle spasms and controlling nausea and stimulating appetite</td>
<td>• Possible anti-inflammatory, analgesic, anti-nausea, anti-emetic, anti-psychotic, anti-ischemic, anxiolytic and anti-epileptic effects</td>
</tr>
</tbody>
</table>

TIP: The ratio of **CBD** (cannabidiol) to **THC** (tetrahydrocannabinol) in the plant influences the therapeutic effects.

The Trichomes
Cannabinoid Availability in Canada

Two Classes of Cannabinoids available for patients:

- Pharmacologic cannabinoid preparations:
  - Nabilone (Cesamet)
  - Sativex (Nabiximols)
- Herbal Cannabis, extracts and derivatives
Nabilone (Cesamet)

- A **synthetic cannabinoid** that is a strong CB1/2 receptor agonist
- Covered by most public and private insurance plans (ODB/ODSP/WSIB) with no LU code needed
- Posology of 0.25 mg, 0.5 mg and 1 mg (0.25 not usually covered)
- Max recommended daily dosage is 6 mg
- Indications: Management of severe nausea/vomiting associated with chemotherapy
- Usually used “off label” and need to inform patients
Nabilone (Cesamet)

Most Common Side Effects:
- Drowsiness (66%)
- Vertigo/Dizziness (59%)
- Euphoria (38%)
- Dry mouth (22%)
- Depression (15%)
- Ataxia (13%)
- Visual Disturbance (13%)
- Concentration difficulties (12%)

Other side effects noted in my patient population:
- Constipation (has been beneficial for IBS/Diarrhea predominant)
- Abdominal pain/bloating
- Tremor
- Confusion/Depersonalization
Nabilone (Cesamet)

- Similar effects to THC
- Due to sedative side effect usually initiated at night
- Typical strategy when starting Nabilone is to titrate up to 1 mg TID
- Encourage patient to write down their symptoms and to experiment with dosages and timing if unable to tolerate recommended dosing schedule
- Provide follow up in 4-6 weeks to monitor response
- Do not change other medications until you see what response they have to Nabilone (potential A/E from withdrawing other meds)
- Does not test positive for THC in urine drug screen
- It is considered a narcotic therefore all standard information has to be on the prescription including total number of caps.
Nabilone (Cesamet)

Sample prescription:
Nabilone 0.5 mg caps
1 cap mg HS x 5 days then
1 cap AM and 1 cap HS x 5 days then
1 cap TID x 5 days then
1 cap AM and Aft., 2 caps HS x 5 days then
1 cap AM and 2 caps Aft. and HS x 5 days then
2 caps TID x 35 days
M: 285 (two hundred eighty five)
Dispense 50 initially and then remainder after 20 days
Sativex (Nabiximols)

- Although a pharmaceutical cannabinoid it is classified as a “Phytocannabinoid”
- Extract from the herbal cannabis plant in an oral-mucosal spray
- Has standardized dose of THC and CBD; 2.7 mg THC and 2.5 mg CBD per spray
- Has all the other “minor cannabinoids” as well as terpenes and flavonoids
- Indicated as adjunctive therapy for symptomatic relief of spasticity and/or neuropathic pain in adults with MS, and for analgesia in patients with cancer on high doses of opioid treatment.
- Covered under some private insurance plans, not covered as a general drug benefit or under ODSP/WSIB. 270$ per bottle, usually sold in packs of 3
- Acts as a tincture, more rapid onset of action than Nabilone, easy to titrate
- Usual dose is 1-2 sprays up to six times daily
- Will cause positive UDS for THC
Herbal Cannabis

• No approved clinical indications in Canada
• Not approved as a “medication” by Health Canada
• No standardized dosing
• Variety of strengths (THC < 1 % to THC > 29 %)
What are the differences between synthetic and natural?

<table>
<thead>
<tr>
<th>Nabilone</th>
<th>Herbal Cannabis</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Single molecule</td>
<td>- Over 100 cannabinoids</td>
</tr>
<tr>
<td>- Standardized dosing</td>
<td>- Over 350 terpenes/flavonoids</td>
</tr>
<tr>
<td>- Longer onset of action</td>
<td>- Shorter onset of action (inhaled)</td>
</tr>
<tr>
<td>- Longer duration of action</td>
<td>- Shorter duration of action (inhaled)</td>
</tr>
<tr>
<td></td>
<td>- Easily titrated</td>
</tr>
</tbody>
</table>

**Entourage effect**: A theory that all of the various compounds present in the plant work together in a cooperative manner yielding the best results.
## Cannabinoids in Canada

<table>
<thead>
<tr>
<th>cannabinoid</th>
<th>dosage</th>
<th>type</th>
<th>start dose and titration</th>
<th>approved indications</th>
<th>availability and cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dronabinol/THC (Marinol)</strong></td>
<td>2.5 – 10 mg THC</td>
<td>Oral Capsule</td>
<td>- Oral Capsule</td>
<td>- Start with 2.5 mg qHS and increase up to 10 mg BID</td>
<td>- Approved for chemotherapy induced nausea and vomiting and anorexia associated with HIV/AIDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Approved for chemotherapy induced nausea and vomiting and anorexia associated with HIV/AIDS</td>
<td>- Maximum recommended dose is 6 mg/day</td>
<td>- Available and Cost:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Same indications as Dronabinol</td>
<td>2.5 mg capsule: $ 2.05 pd 5.0 mg capsule $ 4.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No longer available in Canada</td>
</tr>
<tr>
<td><strong>Nabilone (Cesamet)</strong></td>
<td>0.25 – 1 mg THC</td>
<td>Oral capsule</td>
<td>- Oral capsule</td>
<td>- Start with 0.5 mg qHS and slowly titrate to 1 mg BID</td>
<td>- Available and cost:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Maximum recommended dose is 6 mg/day</td>
<td>0.25 mg capsule: Not covered 0.5 mg capsule $ 0.77 per cap</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.0 mg capsule: $ 1.55 per cap</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Available via ODB, no LU code needed</td>
</tr>
<tr>
<td><strong>Nabiximols (Sativex)</strong></td>
<td>2.5 mg THC + 2.5 mg CBD</td>
<td>Oromucosal spray</td>
<td>- Oromucosal spray</td>
<td>- Start at 1 spray every 4 hrs to a maximum of 4 sprays on day 1 and increase as tolerated</td>
<td>- Available and Cost:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Average dose is 5 sprays/day; limited experience with doses higher than 12 sprays/day</td>
<td>3-5 per spray</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not covered via ODB</td>
</tr>
<tr>
<td><strong>Herbal Cannabis</strong></td>
<td>THC &lt; 0.5 % to &gt; 27 % CBD 0 % to 9 %</td>
<td>Authorized use via Marihuana for Medical Purposes Regulations (MMPR – Health Canada)</td>
<td>- Authorized use via Marihuana for Medical Purposes Regulations (MMPR – Health Canada)</td>
<td>- Average 1-2 grams per day (~ 2 – 4 joints)</td>
<td>- Available and Cost:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 $ - 12 $ per gram</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Available from Licensed Producers approved by Health Canada</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No coverage (Veterans Affairs)</td>
</tr>
</tbody>
</table>
Medical Cannabis in Canada
A Historical Perspective

• In 2001 court challenge requiring the Government of Canada to set up framework by which patients could get a legal supply of medical cannabis

• Marihuana Medical Access Regulations (MMAR) introduced in 2001.

• Under MMAR patients could obtain cannabis from one of three legal methods:
  • From Health Canada
  • Grow their own
  • Have a “Designated Grower” grow for them

• Patients also obtained cannabis in other ways:
  • Compassion clubs or “dispensaries”
  • From the “street”
Historical Perspective

- MMAR required physicians to fill out a form stating that the patient was using herbal cannabis... it was not a prescription. The document would be sent to Health Canada who would approve the patient’s use of herbal cannabis and would provide them with an “Authorization to Possess” card, or ATP.

- The Results: Program grew from 500 patients in 2001 to over 30,000 in 2013. It was believed that change was needed as the program was becoming unmanageable and rife with abuse.
MMPR
Marihuana for Medical Purposes Regulations

- Health Canada overhauled the regulations by which patients were able to access herbal cannabis in 2013. The regulations are now simplified but it now makes physicians the “gatekeepers”.
- No longer forms to fill out that go to Health Canada
- Under the MMPR patients are able to get access to herbal cannabis, with a “medical document” (a.k.a prescription) from their doctor
Only way to legally obtain medical cannabis is through licensed producers (LPs)

LPs are authorized by Health Canada to produce and sell herbal cannabis (oils and fresh leaves and buds soon)

LPs have to demonstrate compliance with regulatory requirements (quality control, records, security)

Dispensaries and compassion clubs are (still) not legal
Pt consults authorized HCP

HCP provides medical document

Pt registers with LP and places order

LP sends medical cannabis to Pt

Pt = patient
HCP = healthcare provider
LP = licensed producer
Marihuana for Medical Purposes Regulations (MMPR)

- Effective as of June 2013
- No more categories, no need for support of specialist
- Provide patient with “medical document”
- Patient submits medical document to a licensed producer approved by Health Canada
- Medical marihuana mailed to patient directly by licensed producer
- Doctor allowed to transfer MMJ to patient (with written consent)
- So far 25 licensed producers approved
The Medical Document (AKA The Prescription)

The Medical Document must include:

- The healthcare practitioner’s name, profession, business address, telephone and fax numbers, and email address
- The healthcare practitioner’s license information
- The patient’s name and date of birth
- The address of the location at which the patient consulted with the practitioner
- The daily quantity (in grams) of marijuana to be used by the patient
- The period of use (up to 12 months)
Know the regulations of their College (CPSO recommendations published March 2015)

Have a meaningful consent discussion around current evidence, lack of rigorous clinical trials and off label usage.

Document reasons for using medical cannabis or cannabinoids (failure of previous treatment, adverse side effects)

Physicians are not obliged to complete a medical document for medical marijuana.

Educate yourself about existing data if you want to prescribe cannabinoids.
CPSO

• Medical Document = Prescription
• Assess risk vs. benefit
• Do not prescribe < 25 unless exhausted all first line treatments
• Informed consent and treatment agreement are needed if writing a medical document
• Specify quantity and % THC on the medical document
• Discontinue if treatment fails to meet goals
• No fees can be charged as this is an insured service
College of Family Physicians of Canada

- Guidance document published Sept 2014 by the CFPC to guide family physicians
- Team of physicians, many coming from addictions and chronic pain background
RECOMMENDATION 4

Dried cannabis is not appropriate for patients who:

a) Are under the age of 25 (Level II)
b) Have a personal history or strong family history of psychosis (Level II)
c) Have a current or past cannabis use disorder (Level III)
d) Have an active substance use disorder (Level III)
e) Have cardiovascular disease (angina, peripheral vascular disease, cerebrovascular disease, arrhythmias) (Level III)
f) Have respiratory disease (Level III) or
g) Are pregnant, planning to become pregnant, or breastfeeding (Level II)

RECOMMENDATION 5

Dried cannabis should be authorized with caution in those patients who:

a) Have a concurrent active mood or anxiety disorder (Level II)
b) Smoke tobacco (Level II)
c) Have risk factors for cardiovascular disease (Level III) or
d) Are heavy users of alcohol or taking high doses of opioids or benzodiazepines or other sedating medications prescribed or available over the counter (Level III)
## Side Effects of Cannabis

<table>
<thead>
<tr>
<th>Most Common</th>
<th>Common</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>Euphoria/”High”</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Blurred vision</td>
<td>Depression</td>
</tr>
<tr>
<td>Somnolence</td>
<td>Postural hypotension</td>
<td>Ataxia</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Vasodilation (Red Eyes)</td>
<td>Asthenia</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>Cognitive effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachycardia</td>
</tr>
</tbody>
</table>

Note: Most of the side effects are a result of THC and some can be attenuated by CBD
Cannabis and Youth

- Increased risk of addiction
  - Unlike other substances the commonest to seek treatment is < 20 years old
  - 35% of young cannabis users have > 1 criteria for dependence
- In those at risk, younger age of first cannabis use is associated with younger age of schizophrenia and bipolar disorder
- Regular users < 18 years old have increased risk of persistent cognitive effects
- Regular use in youth associated with increased social dysfunction, anxiety and depression
Driving

• 4.6% of Canadian users report driving under the influence at least once
• Cannabis intoxication increases the risk of collision related morbidity and mortality up to 3 fold
• Users should not drive:
  • For at least 4 hours after inhalation
  • For 8 hours following use if euphoria experienced
• The ability to drive or perform activities requiring alertness may be impaired for up to 24 hours following a single consumption
Clinical Pearls

- The Endocannabinoid System is under investigation and may have clinical implications in a wide variety of pathologic states.
- Cannabinoids should be considered a therapeutic class with several pharmacologic options.
- Consider prescribing Nabilone or Sativex prior to authorizing the use of herbal cannabis for medical purposes.
- Although having a low risk for mortality, they may cause intoxication and put patients in danger if driving or occupying safety sensitive positions.
- If considering integrating cannabinoids into clinical practice: be comfortable with available evidence, science and recommendations from governing bodies.
- Have a meaningful consent discussion is considering prescribing herbal cannabis.
- Discourage herbal cannabis in youth < 25 years.
Questions?
Further Resources

- Health Canada's document *Information for Health Care Professionals; Cannabis (marihuana, marijuana) and the cannabinoids*
  Available at: http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php

- Canadian Consortium for the Investigation of Cannabinoids (CCIC), free membership at www.ccic.net

- Canadian Journal of Addiction Medicine, Volume 4, number 3, September 2013; *Special Edition: Medical Marijuana, Furthering an Objective Debate.*
  Available at: http://www.csam-smca.org/member-area/cjam-journal/